(FILE 'HCAPLUS' ENTERED AT 11:41:05 ON 12 MAY 2004)

L1 132367 SEA FILE=HCAPLUS ABB=ON PLU=ON (ARRAY OR APPARAT? OR DEVICE OR EQUIPMENT) AND (WELL OR WELLED OR PARTITION?)

L2 12672 SEA FILE=HCAPLUS ABB=ON PLU=ON L1 AND (CRYSTAL? OR RECRYSTAL? OR PRECIPITAT?)

L3 468 SEA FILE=HCAPLUS ABB=ON PLU=ON L2 AND SOLVENT

L4 7 SEA FILE=HCAPLUS ABB=ON PLU=ON L3 AND (BP(S)BOIL? OR BOIL?(W)(PT OR POINT))

L5 5 SEA FILE=HCAPLUS ABB=ON PLU=ON L4 AND (ACID OR BASE OR AMINE OR SALT)

L6 5 SEA FILE=HCAPLUS ABB=ON PLU=ON L5 AND (METHOD OR TECHNIQUE)

L7 3 SEA FILE=HCAPLUS ABB=ON PLU=ON L6 AND (PHARMACEUT? OR COMPOSITION OR DRUG OR FORMULAT?)

L7 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN

ED Entered STN: 21 Feb 2003

ACCESSION NUMBER: 2003:133581 HCAPLUS ← Same as L81 Ans. 2-20

DOCUMENT NUMBER: 138:180672

TITLE: **Apparatuses** and **methods** for creating and testing pre-**formulations** and systems for same

INVENTOR(S): Carlson, Eric D.; Cong, Peijun; Chandler, William H., Jr.; Chau, Henry K.; Danielson, Earl; Desrosiers, Peter J.; Doolan, Robert D.; Wu, Luping

PATENT ASSIGNEE(S): Symyx Technologies, Inc., USA

SOURCE: PCT Int. Appl., 229 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003014732	A1	20030220	WO 2002-US16962	20020524
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003116497	A1	20030626	US 2002-156245	20020524
US 2003119060	A1	20030626	US 2002-156295	20020524
US 2003118078	A1	20030626	US 2002-156329	20020524
US 2003124028	A1	20030703	US 2002-156222	20020524

PRIORITY APPLN. INFO.: US 2001-311332P P 20010810

AB The invention provides **methods, apparatus,** and systems for performing high-throughput preparation and screening of **salts** and polymorphs of **drug** candidates. The

invention is directed towards enhancing the pre-**formulation** discovery process used for **drug** development. In particular, processes that determine suitable **salts** and processes that discover substantially every polymorph that can form from a particular **drug** candidate are provided. The processes are performed using several **apparatuses** that are specifically configured to carry-out various steps in a high-throughput characterization process. One such **apparatus** is configured for synthesizing a plurality of library members based on, for example, a library model generated by a computer system.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 16 Dec 2001
ACCESSION NUMBER: 1908:11195 HCAPLUS ← same as L81 Ans. 18-20
DOCUMENT NUMBER: 2:11195
ORIGINAL REFERENCE NO.: 2:2482f-i,2483a-i
TITLE: Contribution to the Knowledge of Gelatinization Processes, I and II
AUTHOR(S): Levites, S. Ya.
CORPORATE SOURCE: Chem. Lab. Kaiserl, Inst. f. Expt. Med, St. Petersburg
SOURCE: Zeitschrift fuer Chemie und Industrie der Kolloide (1908), 2, 208-15,237-41
CODEN: ZCIKAL; ISSN: 0372-820X
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable

AB (1) Certain factors influence the condition of a dissolved substance. The same material may be dissolved as a **crystalloid** in one **solvent** and as a colloid in another, e. g., **salts** of the higher fatty **acids** dissolve in water as colloids and in alcohol as **crystalloids** . The concentration of the solution has a similar influence, substances such as sodium palmitate and sodium silicate acting as **crystalloids** in dilute solution and as colloids in more concentrated solutions. According to many the colloidal solution is not a true solution in the sense of the present solution theory, but is a pseudo-solution, the dissolved body being in the form of small submicroscopic particles. As far as conformation to the laws of boiling and freezing points is concerned, colloids form only pseudo-solutions. If, however, we define solution as a simple homogeneous mixture, the **composition** of which can be varied within certain limits, then we have a definition not dependent on the state of aggregation, and a colloidal solution would come under this definition. The gelatinization process is not a sudden change from liquid to jelly, but proceeds with greater or less velocity, depending on the nature of the solution and other conditions. No sharp line can be drawn as in the change from liquid to solid phases. The gradual change is **well** indicated by the gradual change of the viscosity of the solution. Observations on the viscosity of gelatinizing colloidal solutions, and on non-gelatinizing solutions of glutin, agar-agar, alkaline casein solution, and water solutions of albumin and commercial peptone, made with the Ostwald **apparatus** and calculated according

to the equation n = ts/t1s1 where 1 is the time the unknown solution takes to run out, s its specific gravity, and 11S1 the same for water, are recorded. The influence of concentration and temperature, and of foreign substances, on the viscosity of colloidal solutions was first studied. The viscosity increases with increased concentration. In concentrated solutions the Arrhenius formula, n = Ax where A is a constant and x the concentration of the solution, agrees with the experimental observations, but in more dilute solutions (0.5-1.5%) the linear equation n = 1 + an shows best agreement. Glutin heated in a closed flask for some time at the **boiling point** of water loses its capacity to gelatinize, and if it be **precipitated** from the solution with alcohol and ether, an amorphous mass results which is readily soluble in water, called P-glutin. Such P-glutin shows a lower viscosity than ordinary glutin. A rise of temperature decreases the viscosity of a solution and a lowering of temperature increases it, but gelatinizing colloidal solutions show a constant value only under definite temperature conditions. For a colloidal solution of definite concentration there is a temperature minimum below which the viscosity gradually increases till gelatinization takes place. The viscosity is assumed to be constant if inside of three hours it changes not more than 0.15-0.20%. The viscosity of a solution can remain constant only when there is one homogeneous liquid phase; when a second solid phase appears the homogeneity is destroyed and the viscosity ceases to be constant. The increase in viscosity is proportional to the rate of formation of the solid phase. The **method** of studying the influence of foreign bodies on the viscosity was as follows: to study the effect of N KI solution on 1.5% glutin solution 25 cc. of a 3% glutin solution are mixed with 25 cc. of a 2N KI solution, all solutions being at the same temperature. Tabulated results show that all materials which decrease the viscosity of water also decrease the viscosity of the colloidal solution, and all which increase the viscosity of water also increase the viscosity of the colloidal solution. This rule holds for very different organic colloids so long as there is no chemical action of the foreign body. NaNO3 is an exception, causing a decrease where one would expect an increase in the viscosity of agar-agar solution. The results on gelatinizing solutions are the same provided we are dealing with one homogeneous phase. The nature of the **crystalloid** admixture has an influence on the temperature minimum at which the viscosity is constant, some decreasing it while others raise it. The effect of the introduction of a **crystalloid** into a solution of another **crystalloid** has been studied by Rudorf (Z. physik.Chemical, 1903, 43) who finds cases analogous to the colloid and **crystalloid** mixtures. The influence of the **crystalloid** is independent of the number of colloids in the solution. Egg albumin and Witte-peptone conduct themselves the same as glutin. If the mixture contains more than one **crystalloid** or if there is a chemical action of the colloid and **crystalloid** then the rule does not hold. Different **salts** added to alkaline casein solution give a mixture with a viscosity differing widely from the added viscosities of the two solutions. All inorganic **salts** used decreased the viscosity of the casein solution, while sodium **salts** of acetic, salicylie, and benzoic **acids** gave variable

LANGUAGE: Japanese
STATUS: New
AB New artificial receptors based on calix¢5!arene for Buckminsterfullerene and neutral guest molecules are reported. Calix¢5!arene derivatives form inclusion complexes with C60 in a variety of organic **solvents** such as toluene, benzene, CS2, and o-dichlorobenzene. The association constants of the complexes were determined by using Benesi-**Hildebrand** method. The structure of the complex in the solid state was disclosed by X-ray **crystallography**. 13C signal of C60 in the presence of the host molecule exhibits 0.35ppm up-field shifts. This result indicates that C60 bound within the cavity of the host molecule. "Upper rim" functionalized calix¢5!arene having two benzoic **acid** moieties is synthesized. The host molecule binds neutral guests, such as 9-ethyladenine, 2-aminopyrimidine, and imidazole, by the use of hydrogen bonding interaction. The association constants were determined by 1H-NMR titration using a non-linear least squares method. The structures of the complexes were predicted by molecular mechanics calculation using MacroModel V. 4.5. (author abst.)

L93 ANSWER 5 OF 6 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 84021476 EMBASE
DOCUMENT NUMBER: 1984021476
TITLE: Isocratic chromatographic retention data for estimating aqueous solubilities of acidic, basic and neutral drugs.
AUTHOR: Hafkenscheid T.L.; Tomlinson E.
CORPORATE SOURCE: Physical Pharmacy Group, Department of Pharmacy, University of Amsterdam, 1018 TV Amsterdam, Netherlands
SOURCE: International Journal of Pharmaceutics, (1983) 17/1 (1-21).
CODEN: IJPHDE
COUNTRY: Netherlands
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
LANGUAGE: English
AB For 108 compounds of diverse chemical character (including drug molecules) isocratic reversed-phase liquid chromatographic retention parameters have been used in modifications of the **Hildebrand** -Scott equation to estimate compound acqueous solubility. The relationships found are valid for both liquids are **crystalline** solids, as well as for stronger (pK(a) > 6.5) bases that are chromatographed in a partially ionized state. It is observed that there is a significant constant difference in behaviour between **acid** and alcohol molecules and neutral and base molecules. This difference can be empirically corrected for during solubility estimations. Comparison of the use of octan-1-ol/water distribution coefficients in these equations shows that the use of isocratic chromatographic retention parameters lead to significantly better estimations of compound aqueous solubility.

L93 ANSWER 6 OF 6 MEDLINE on STN

ACCESSION NUMBER: 81143965 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7205222
TITLE: Extended solubility approach: solubility parameters for **crystalline** solid compounds.
AUTHOR: Martin A; Carstensen J
SOURCE: Journal of pharmaceutical sciences, (1981 Feb) 70 (2) 170-2.
Journal code: 2985195R. ISSN: 0022-3549.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198105
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19900316
Entered Medline: 19810528

AB A method is suggested to obtain solubility parameters for **crystalline** solid compounds involving a quadratic equation based on the original Scatchard-**Hildebrand** solubility expression. The geometric mean delta 1 delta 2, of the **Hildebrand** approach is replaced by w12 = K delta 1 delta 2, and log alpha 2/(V2 phi 2(2)/2.3RT) is regressed against delta 1 in a second-degree power series for parabens and benzoic **acid** in a series of normal alcohols. The method provides reasonable solubility parameters for the solid solutes and affords a convenient calculation of the solubility of drugs in a homologous series of **solvents.**

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results. The influence of the **crystalloid** is dependent on the anion. (II). See following abstract.

L7 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 16 Dec 2001
ACCESSION NUMBER: 1907:1700 HCAPLUS ← Same as L81 Ans. 20-20
DOCUMENT NUMBER: 1:1700
ORIGINAL REFERENCE NO.: 1:437g-i,438a-i,439a-i,440a-i,441a-d
TITLE: A **Method** for the Separation and Determination of Chlorophyl Derivatives
AUTHOR(S): Willstatter, Richard; Mieg, Walter
CORPORATE SOURCE: Chem. Lab., Konigl. Akad. Wissenschaften, Munchen
SOURCE: Ann. (1907), 350, 1-47
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB The author's **base** their **method** upon the peculiar basic nature of many chlorophyl derivatives and apply it to two series of compounds, the one comprising products obtained by the action of alkali on a chlorophyl extract and derivatives obtained from them by the action of **acids**, the second consisting of products obtained principally from alkachlorophyl by treatment with alcoholic hydro-chloric **acid**. The first form olive-green to green solutions in indifferent **solvents**, blue-green to green solutions with **acids**. The second show similar color in **acid** solutions, but in neutral solutions are a brilliant red. The series are named respectively the phytochlorines and the phytorhodines and the individual members designated provisionally phytochlorine a, phytochlorine b, etc. The phytochlorines and phytorhodines are insoluble in water, more or less soluble in organic **solvents**. As weak **acids** they dissolve in alkalies and may be completely extracted from ether solution even by ammonium hydroxide or sodium bicarbonate. They contain no phenolic hydroxyl and but a single esterifiable **acid** group. Their esters are insoluble in alkalies. All are weak **bases** whose **salts** are completely decomposed by water. Unlike the **acid** properties, however, the basic properties show differences and gradations, differing from any yet described in connection with weak organic **bases**. To extract these substances from ether solution by means of hydrochloric **acid** it is necessary to use **acid** of a definite minimum concentration and by treating the ether solution of a mixture of the phytochlorines, for example, successively with hydrochloric **acid** solutions of increasing concentration it is possible to effect a very satisfactory separation and eventual purification of the individual members of the series. The following tables illustrate the differences in solubility upon which the separation **methods** are based: Traces go into solution in hydrochloric **acid** of,Dissolved very freely in hydrochloric **acid** of,Dissolved almost completely in hydrochloric **acid** of;Phytochlorine a.....,3.5%,6.5%,7.5%;", b.....,1.5%,3.5%,5.0%;",c.....,0.5%,1.5%,2.0%; ",d.....,0.15%,0.5%,1.0% On shaking ether solutions of phytochlorines a and b with equal volumes of hydrochloric **acid** of varying concentration the following results were obtained: Phytochlorine,Hydrochloric **acid** of,Percentage of

substance dissolved;a.....,8.0%
,84.1;a.....,7.0%,73.8;
a.....,6.0%,60.7;
b.....,5.5%,74.4;
b.....,4.0%,54.7;
b.....,2.5%,26.4 The colors of the various solutions and extracts give useful indications of the quality and quantity of the substances present. Four closely related phytochlorines of differing basicity, but exhibiting similar colors in neutral, **acid** and alkaline solutions were obtained. The more strongly basic members show fluorescence as **well** as more pronounced color. The solubility in many **solvents**, e. g., alcohol and benzene, decreases with the increase in basic properties. All are unstable toward oxidizing and reducing agents, and are very easily changed by heat, apparently with loss of water. The phytorhodines, of which five (two in impure condition) were obtained from a somewhat similar series, differ from the phytochlorines principally in giving red instead of green solutions in ether. It proved difficult to prepare the substances for analysis and the empirical formulas could not be established with certainty. The analytical results, however, point to close similarity in **composition**. Some of the compounds seem to be isomers, as phytochlorines a and b, phytorhodine a and phytochlorine d, etc. Others, as phytochlorines a and d, seem to differ by the elements of a molecule of water. The authors interpret their analytical results provisionally by assuming three atoms of nitrogen present in the molecules of all of these chlorophyl derivatives and thus arrive at the following formulas for the more important members of the series: Phytochlorine a .....,C23H33O6N3;",b .....,C28H33O6N3;",c .....,C28H33O6N3;",d .....,C23H33O6N3;Phytorhodine a ....., C25H33O6N3;Ethyl ester of phytorhodine a .....,C30H37O6N3;Phytorhodine b .....,C28H33O4N3;Ethyl ester of phytorhodine b .....,C30H37O4N3 Attempts to determine the molecular weights of the compounds by the **boiling point method** were fruitless, but an analysis of the cesium **salt** of phytochlorine b gave a result not inconsistent with the above assumption. The new compounds do not correspond to any of the chlorophyl derivatives hitherto reported. While phytochlorines a and b are very similar to E. Schunk's phyllotaonine [Pr. Roy Society, 44, 448 (1888), and 55, 351 (1894); Ann., 278, 329 (1894)] and certain of the phytorhodines resemble the phylloporphyrine of E. Schunk and L. Marchlewski [Pr. Roy. Society, 57, 314 (1895); Ann., 284, 81 (1894)], even a close relationship between these, to say nothing of their identity, is excluded by a comparison of the results of their analyses. EXPERIMENTAL RESULTS. The chlorophyl extracts from which the phytochlorines were obtained were prepared by boiling dried nettle leaves with alcohol or ethyl acetate in a stone-ware extraction **apparatus** and were found to contain relatively little unchanged chlorophyl. Portions of the extract were boiled under a reflux **apparatus** with ten parts of a 2% solution of potassium hydroxide in 95% alcohol and, after cooling the mixture,

diluting **well** with water and neutralizing with hydrochloric **acid**, the reaction products were extracted with ether. The longer the digestion with alcoholic potassium hydroxide solution continues, the more phytochlorine b and the less phytochlorine a are obtained, owing to the conversion of the latter into the former by the continued action of the alcoholic potash. A digestion of about fifteen minutes gives the best relative yield of phytochlorine a. The ether extract of the reaction products is shaken with 17% hydrochloric **acid** whereby phytochlorines a and b are separated from indifferent and less basic substances. The phytochlorines are recovered by neutralizing the hydrochloric **acid** solution and again extracting with ether. On shaking this second ether extract with 3% hydrochloric **acid**, phytochlorine b passes into solution in the hydrochloric **acid** accompanied by only traces of phytochlorine a. (For full details of the **method** of separation and purification reference must be made to the original). Phytochlorine a **crystallizes** from benzene, ether or alcohol in rosettes of fine hard needles of bluish black color and metallic lustre which m. with partial alteration at 181-182°. The results of the analysis agree fairly **well** with the formula, C26H18O6N3. Drying the preparation in a toluene bath or long continued heating with **solvents** causes the loss of half a molecule of water which is restored on again shaking with ether and water. The dehydrated preparation m. above 200°. Solutions of phytochlorine a in ether and in alcohol show olive-green color and moderately strong red fluorescence. In glacial acetic **acid** solution the color is a brilliant blue accompanied by strong red fluorescence. Phytochlorine a possesses weakly basic and marked **acid** properties. It is almost completely extracted from ether solution by 8% hydrochloric **acid**, scarcely at all by 3% **acid**. The hydrochloric **acid** solutions are deep bluish green, appearing red by transmitted light, but show no fluorescence. Alkaline solutions, even sodium bicarbonate, extract phytochlorine a completely from its ether solution. The resulting solutions are olive-brown and without fluorescence. Boiling phytochlorine a with a methyl alcohol solution of hydrogen chloride converts it apparently into an ester. Oxidizing and reducing agents decolorize it. Digestion with alcoholic potash converts it completely into phytochlorine b. Phytochlorine b shows the same colors and fluorescence in indifferent **solvents** as phytochlorine a, but its acetic **acid** solution is light violet-blue. It forms bluish black **crystals** with metallic lustre which m. with decomposition at 183-190°. Analysis points to the same formula as for phytochlorine a. It shows the same behavior toward alkalies but is more basic than phytochlorine a, being partially extracted from ether solution by even 2% hydrochloric **acid** and almost completely by 5%. A cesium **salt** containing 21.8% cesium was prepared, but did not seem to be a pure primary **salt**. Hence, no definite conclusions regarding the molecular weight could be drawn from its **composition**. By boiling phytochlorine b with a concentrated solution of hydrogen chloride in methyl alcohol a compound without **acid** properties was obtained in the form of steel-blue **crystals** which underwent no change on heating in the toluene bath and m. fairly sharply at 140°. The results of the

analysis were consistent with the assumption that the compound was a methyl ester of phytochlorine b formed with simultaneous loss of one molecule of water between two molecules of the phytochlorine [=(C28H24O4.8N3)2]. From this an **acid** saponification product was obtained having the properties of phytochlorine b. The ester was less basic than the phytochlorine. Phytochlorines a and b on standing with concentrated hydrochloric **acid** generally go over into a series of new compounds which differ from the above described phytochlorines in the more markedly green color of their ether and the blue color of their hydrochloric **acid** solutions. Of these only the two most basic, phytochlorines c and d, are described. They were separated by fractionation with 0.5% and 1.5% hydrochloric **acid**. Phytochlorine c is readily extracted from ether by 2% hydrochloric **acid**. It dissolves in dilute alkalies with a green, in dilute **acids** with a blue color, both solutions showing red fluorescence. The preparations showed no definite melting points. Analysis makes the formula, C23H14O8N3, probable. Phytochlorine d is characterized by the most brilliant colors. It is the strongest **base** and the weakest **acid** of the series. It differs from the other phytochlorines in dissolving in water, the resulting violet solution showing strong red fluorescence. This water-soluble form, however, seems to exist only in the absence of **acids**. From its solutions in alkalies, after large dilution with water, it may be extracted by ether, while 1% hydrochloric **acid** extracts it very completely from its ether solution. The hydrochloric **acid** solution is strongly fluorescent. The dry substance is readily subject to change on heating and even on standing and so has no definite m. p. and could not be prepared for analysis in its original form. The analysis of a long dried preparation indicated the formula, C28H23O6N3. Preparation of the Phytorhodines. From an alcoholic extract of unchanged chlorophyl prepared without heating two alkachlorophyls were obtained, the first by **precipitation** with potassium hydroxide and filtering, the second from the filtrate by **precipitation** with alcoholic calcium chloride solution. On heating with alcoholic hydrochloric **acid** these alkachlorophyls yielded two closely related but different series of phytorhodines. From the potassium compound were obtained by extraction with ether, treatment with dilute alkali and fractionation by hydrochloric **acid** of graded concentration, phytorhodine a (together with two similar but stronger **bases**), the ester of phytorhodine a, and phytorhodine d, insoluble in ether. From the calcium alkachlorophyl, phytorhodine b, its ester, a stronger **base** , phytorhodine c and phytorhodine e, insoluble in ether, were similarly obtained. The yields throughout were very small. Phytorhodine a in indifferent **solvents** shows a carmine-red color with little fluorescence, in hydrochloric **acid** solution bluish green with slight red fluorescence. It requires 7.5% hydrochloric **acid** for its complete extraction from ether. M. indefinitely between 130°-140°. Analysis indicates the formula, C28H23O6N2. The ethyl ester of phytorhodine a, insoluble in alkalies but more weakly basic than phytorhodine a, requires 9.5% hydrochloric **acid** for its extraction from ether. Alcoholic potash or hydrochloric **acid** saponifies it, regenerating phytochlorine a. The **acid** solution of

the ester is violet-green with slight red fluorescence, the ether solution brilliant carmine and more strongly fluorescent. Its **crystals** liquefy under 100° without showing a sharp m. p. Analysis indicates the formula, C28H25O6N3. Phytorhodine b shows purple-red color and fluorescence in ether solution, violet-blue with red fluorescence in **acid**. It is a weaker **base** than phytorhodine a, requiring 9% hydrochloric **acid** for its extraction from ether. It **crystallizes well** but has no sharp m. p. Very dilute sodium hydroxide **precipitates** brown flocks from its ether solution. Analyses leads to the formula, C28H25O6N3. Its ethyl ester shows the same colors in solutions, but is less basic. It **crystallizes well**, but m. with decomposition at 76-80°. Analysis points to C30H37O4N3. Phytorhodine b may be regenerated from it by saponification. Phytorhodine c is much more strongly basic than the b compound, but shows similar colors in solution. It is accompanied in the reaction product by a still stronger and very highly colored **base**. The authors regard the analysis as indicating the formula, C34H26O9N6. Phytorhodines d and e, weakly basic and insoluble in ether, accompany a and b, respectively. The hydrochloric **acid** solution of the former shows a changeable violet-green color, that of the latter a changeable violet-blue, both with fluorescence. The analyses indicate (C28H26O5.5N3)2 for d and C28H31O4N3 for e. Phytorhodine f accompanies phytochlorines a and b and is separated from the ether solution after their extraction, but displays the characteristic colors of the phytorhodines. The results of the analysis lie between C28H26O6N3 and C28H29O4N3. The compound is stable toward alcoholic potash and toward strong hydrochloric **acid**.
Complex Compounds with **Salts**. The phytochlorines and the phytorhodines both form two series of double compounds with metallic acetates, one set in each case being insoluble in ether, the other soluble. The copper and the zinc compounds are very intensely colored. The ether solutions of the zinc double **salts** fluoresce strongly. The zinc **salts** are dissolved and decomposed into their constituents by 10-20% hydrochloric **acid**, but the copper **salts** require concentrated **acid** for their solution and then are not decomposed.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, PASCAL, FEDRIP, DISSABS' ENTERED AT 11:44:11 ON 12 MAY 2004)

L8 1 S L7 ← Same as L83 Ans. 8-26

L8 ANSWER 1 OF 1 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2002-750607 [81] WPIDS
DOC. NO. NON-CPI: N2002-591116
DOC. NO. CPI: C2002-212774
TITLE: New determination **method** of multicomponent chemical **composition**(s) comprises selecting experimental parameters, causing **apparatus** to conduct experiments, and selecting multicomponent chemical **compositions** of matter based on results.
DERWENT CLASS: B04 C07 D14 J04 T01
INVENTOR(S): CHIN, D; LEVINSON, D A

PATENT ASSIGNEE(S): (CHIN-I) CHIN D; (LEVI-I) LEVINSON D A; (TRAN-N) TRANSFORM PHARM INC
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002077772	A2	20021003	(200281)*	EN	62
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG UZ VN YU ZA ZM ZW					
US 2002177167	A1	20021128	(200281)		
EP 1381857	A2	20040121	(200410)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002077772	A2	WO 2002-US9274	20020325
US 2002177167	A1 Provisional	US 2001-278401P	20010323
		US 2002-103983	20020322
EP 1381857	A2	EP 2002-733893	20020325
		WO 2002-US9274	20020325

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1381857	A2 Based on	WO 2002077772

PRIORITY APPLN. INFO: US 2001-278401P 20010323; US 2002-103983 20020322

AN 2002-750607 [81] WPIDS

AB WO 200277772 A UPAB: 20021216

NOVELTY - New **method** for determining multicomponent chemical **composition**(s) comprises:

(1) selecting a combination of experimental parameters that may be varied by a high-throughput automated experimentation **apparatus**;

(2) causing the **apparatus** to conduct experiments for each combinations of value(s) of the experimental parameters; and

(3) selecting multicomponent chemical **compositions** of matter based on results.

DETAILED DESCRIPTION - New **method** for the determination of multicomponent chemical **composition**(s) comprises:

(a) selecting a combination of experimental parameters that may be varied by a high-throughput automated experimentation **apparatus**;

(b) determining a first distinct combinations of value(s) of

the experimental parameters, each combination corresponding to a distinct experiment;

(c) causing the automated experimentation **apparatus** to conduct a first set of experiments for each of at least a portion of the first distinct combinations of value(s) of the experimental parameters;

(d) determining a first collection of experimental results of the first set of experiments, the first collection comprising individual result sets, each individual result set corresponding to a distinct experiment;

(e) based on the first collection of experimental results, determining a second distinct combinations of value(s) of the experimental parameters, each combination corresponds to a distinct experiment;

(f) causing the automated experimentation **apparatus** to conduct a second set of experiments for each of at least a portion of the second distinct combinations of value(s) of the experimental parameters;

(g) determining a second collection of experimental results of the second set of experiments, the second collection comprising individual result sets, each individual result set corresponding to a distinct experiment; and

(h) selecting multicomponent chemical **compositions** of matter based on the first collection of experimental results and the second collection of experimental results.

INDEPENDENT CLAIMS are also included for:

(A) a **method** of estimating one or more properties of a multicomponent chemical **composition** comprising:

(1) receiving signals representing an experimental result set for each of the experiments conducted by a high-throughput automated experimentation **apparatus;**

(2) generating a predictive model based on signals characterizing each experimental result set according to the property to be estimated and signals characterizing the experiment with respect to a set of molecular descriptors; and

(3) estimating the property for a multicomponent chemical **composition** by providing signals characterizing the multicomponent chemical **composition** with respect to the molecular descriptors as input to the predictive model;

(B) a system for determining a multicomponent chemical **composition** comprising:

(1) a database comprising table(s) comprising molecular descriptors, compound identifiers, compound/descriptor relations associating portion(s) of the compound identifiers with molecular descriptors, empirically determined physical, chemical and biological parameters, compound/parameter relations associating compound identifier(s) with empirically determined physical, chemical and/or biological parameters, data presenting results from experiments performed with a high-throughput automated experimentation **apparatus;**

(2) a query system for selecting subsets of related information from table(s);

(3) a multidimensional representation generation module capable of generating visual representations of data sets having at least 4 dimensions; and

(4) modeling modules, each module is capable of receiving

information selected by the query system and estimating at least one property of a **formulation**;

(C) a **method** of producing **crystals** comprising:

(1) electronically calculating a set of predicted **crystal** polymorphs of a target compound;

(2) electronically calculating expected experimental results for at least a portion of the predicted polymorphs;

(3) conducting a first **crystallization** experiments using a high-throughput automated experimentation **apparatus**; and

(4) electronically comparing at least a portion of the expected experimental results with the actual experimental results to determine which of the portion of the polymorphs were produced;

(D) a **method** for determining a solid form of a compound comprising:

(1) predicting a crystal structure of a target chemical species;

(2) selecting a first range of conditions for crystal generation;

(3) conducting a first experiments within the first range of conditions using a high-throughput automated experimentation apparatus;

(4) testing at least a portion of the experimental results of the presence of crystals;

(5) classifying at least a portion of the experiments based on predicted crystal forms;

(6) selecting a second range of conditions for crystal generation based on the classification(s); and

(7) conducting second experiments within the second range of conditions using the high-throughput automated experimentation apparatus; and

(E) a method for preparing a crystal comprising:

(1) performing simulated hydrogen-bond-biased simulated annealing to predict polymorphs of a target compound;

(2) calculating expected properties of at least one portion of the predicted polymorphs;

(3) conducting crystallization experiments using a high throughput automated experimentation apparatus;

(4) comparing measured properties of crystals produced by the crystallization experiments with the expected properties of at least a portion of the predicted polymorphs to determine which of the portion(s) of the predicted polymorphs were produced by the experiments;

(5) generating a predictive model of the relationship between experimental parameters and polymorphs produced; and

(6) calculating a set of experimental parameters for a second set of crystallization experiments from the predictive model.

USE - For determining multicomponent chemical composition(s).

ADVANTAGE - The inventive method systematically integrate all available information in a manner that permits the useful deployment of a limited number of experiments to increase or maximize the probability of yielding compounds, compositions or formulations that posses a desired property or set of properties over an expected range of conditions of manufacture, storage, administration and/or use.

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